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Introductory Chapter: Behcet's Disease - An Overview

Müzeyyen Gönül and Selda Pelin Kartal

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1. Introduction

Behçet's disease (BD) is a multisystem inflammatory disease with unknown etiology [1]. It may affect vascular, gastrointestinal, neurologic, articular, pulmonary, cardiac, and urogenital systems [1, 2].

2. History

The disease was first described by a Turkish dermatologist, Hulusi Behçet, in 1937 as a triple symptom complex; aphthous stomatitis, genital ulcers, and relapsing uveitis [2]. Hulusi Behçet was born in 1889 in Istanbul/Turkey. In 1910, he became a medical doctor, and in 1914, he received a dermatologist title. In 1933, he became a professor of dermatology and venereal diseases. Hulusi Behçet is the first academician with a titled professor in the history of Turkish academy. Hulusi Behçet observed aphthous symptoms in the mouth and genital area and several findings in the eye in his three patients whom he followed 21, 7 and 3 years. He believed that this was a new disease. In 1937, he reported his observations in "Dermatologische Wochenschrift" and then he presented his patients in a dermatology meeting in Paris. In later times, same cases were reported from various regions of the world. In 1947, the new disease was named as "*Morbus Behçet*" in International Congress of Geneva [3].

3. Epidemiology

BD has a worldwide distribution. But it is commonly observed in the Silk Road countries between the Mediterranean Sea, including such countries Spain, Portugal, Turkey, Iran, and

Far East countries like China and Japan [4, 5]. The disease is most common in Turkey with the prevalence of 20-602 per 100,000 [6, 7]. It develops at any age, but it most appears between the second and fourth decade of life [8]. BD patients with early onset may have the more severe disease [9]. BD is uncommon in children. Patients with initial symptoms at age 16 years or younger are classified as juvenile-onset BD. The prevalence of juvenile BD is unknown. But in few series, it is reported between 3, 3 and 26% of BD patients were before age of 16 years [10]. BD affects the both gender equally [11]. The disease is more severe among male patients, and vascular disease is the major risk factor of death in male patients. It is shown that vascular disease, folliculitis, papulopustular skin lesions, positive pathergy test, and ocular disease are more common in men while erythema nodosum, genital ulcers, and joint involvement are more common among women [12, 13].

4. Etiology

Although several immunological abnormalities have been demonstrated, the real etiologic mechanism of the disease is unclear.

4.1. Infectious agents

The most probable hypothesis is that in genetically predisposed individuals some infectious agents such as *Herpes simplex virus* (HSV)-1, *Streptococcus sanguinis* (*S. sanguinis*) or some autoantigens such as heat shock proteins (HSP) trigger the autoinflammatory reactions [1]. BD has aspects of both autoimmune disease and auto inflammatory disease. The autoimmunity indicators are the effectiveness of classical immunosuppressives such as azathioprine and cyclosporine, and the suggested role of the candidate autoantigen, human heat-shock protein 60 (HSP60). Also, the lack of significant high-titer autoantibodies or antigen-specific T-cells, strong involvement of major histocompatibility complex (MHC) class I molecules, clinical episodes of unprovoked recurrent inflammation, mainly caused by neutrophils, and the therapeutic effectiveness of colchicine, are signs of autoinflammation [14].

Infection agents have an important role in the pathogenesis of BD. Several investigations have shown the association between HSV and BD. But, in some studies, this association could not be detected [1, 15, 16]. Therefore, the role of HSV at the etiopathogenesis of BD is not clear.

Several potential bacteria have been investigated but the most commonly implicated microorganism is *S. sanguinis* [17]. It was found that Bes-1 gene and HSP-65 derived from oral *S. sanguinis*, are supposed to play important roles as an extrinsic factor in BD pathogenesis. The peptides of the Bes-1 gene are highly homologous with the retinal protein Brn3b, and moreover, the Bes-1 peptides were homologous with HSP-65 derived from microorganisms in association with the counterpart human HSP-60, which appeared reactively in the BD patients. Some homologous peptides of HSP-65 were found to reduce IL-8, IL-12, and TNF- α in active BD patients [18]. Also, it is shown that *S. sanguinis* antigens increase IFN- γ and IL-6 secretion from the peripheral blood cell T cell of BD patients [19].

From another report, it was detected that *Streptococcus mutans* (*S. mutans*) colonization rate was significantly higher in BD. *S. mutans* presence in saliva was associated with oral ulcers, and it was associated with severe disease course than milder disease [20].

Heat shock protein (HSP) functions as an intracellular chaperonin of other proteins and significant sequence homology is found between mammalian HSP and microbial HSP. HSP60/65 was thought to be a major cause of the skewed immune responses in patients with BD because of the molecular mimicry between human HSP and microbial HSP. HSP60 regulates Th1 cell differentiation through multiple immunologic pathways [21].

Gut microbiota compositional alteration may have an association with immune dysfunction in patients with BD. Direct comparison of the relative abundance of bacterial taxa demonstrated that the genera *Bifidobacterium* and *Eggerthella* increased significantly and the genera *Megamonas* and *Prevotella* decreased significantly in BD patients compared with normal individuals. The authors suggested that the compositional changes of gut microbes may be one type of dysbiosis (unfavorable microbiota alteration) in patients with BD. The dysbiosis may have an association with the pathophysiology of BD [22].

4.2. Genetic factors

Genetic factors play important roles in the pathogenesis of BD. Multiple studies have demonstrated that BD is strongly associated with the presence of human leukocyte antigen (HLA)-B5 and its split antigen HLA-B51 [11, 23]. The association with HLA-B5 was first described by Ohno et al. in 1973. Several studies confirmed the HLA-B51 association with BD and HLA-B51 is the strongest known genetic factor for BD [1]. The MHC region on chromosome 6p21 contains HLA and other essential genes in the immune response [14]. A meta-analysis based on 72 studies in 74 study populations revealed the moderate association of HLA-B5/-B*51 with male gender, the high prevalence of eye involvement, skin involvement, and genital ulcers, and low prevalence of gastrointestinal involvement [24]. Some of the other susceptible genes associated with BD are IL10, IL23R-IL12RB2, STAT4, TNFAIP3, CCR1-CCR3, KLRC4, FUT2, IL12A, IL23R, TLR4, MEFV, and NOD2. The genes identified are involved in both innate and adaptive immunity and support the idea that polarization in Th1/Th17 pathway plays a critical role in BD pathogenesis [14].

5. Clinical manifestations

5.1. Mucocutaneous findings

5.1.1. Oral aphthosis (ulceration)

Oral ulceration is the most detected symptom that seen over 97% of the patients. It is a painful, recurrent, round, and oval ulceration with well-defined borders and central yellowish pseudomembrane. An erythematous halo surrounds the ulcers. The most common sites are mucous membranes of the lips, buccal mucosa, tongue, and soft palate. They can be classified

as minor, major or herpetiform on the basis of ulcer size and number. Oral ulcer often resolves spontaneously within 1–4 weeks. Local trauma can trigger new oral ulceration. At the differential diagnosis of oral ulcers herpes simplex, erythema multiforme, fixed drug eruption, MAGIC syndrome, Reiter's syndrome, and Sweet's syndrome, anemia due to a deficiency of iron, vitamin B12 or folic acid, inflammatory bowel diseases, and systemic lupus erythematosus must consider [1, 25, 26].

5.1.2. Genital ulcers

Genital ulcers can be seen 60–89% of the patients. Genital ulcers are similar in appearance to oral ulcers. The scrotum is the most frequently involved site in males. Ulcers can also be observed on the shaft and glans penis. In females, the ulcers most commonly occur on the labia but the vaginal mucosa and rarely the cervix can also be affected. Vaginal ulcers often cause a discharge. GU may occur in both sexes in the groin, perineal and perianal area. They usually heal within 10–30 days and deep ulcers may lead scarring. Genital herpes simplex infection, erythema multiforme, fixed drug eruption, sexually transmitted diseases such as syphilis, chancroid, lymphogranuloma Venereum and HIV infection should be considered in differential diagnosis [1, 25, 26].

5.1.3. Erythema nodosum like lesions

Erythema nodosum like lesions is mostly seen in females. They are characterized by painful multiple subcutaneous nodules that vary in size and color. They are frequently seen at the lower extremities but they can also be localized to the face, neck, forearms, and buttock. The lesions resolve spontaneously within 2–3 weeks. The histopathological features of erythema nodosum-like lesions are characterized by the presence of vasculitis or vascular reaction; different from erythema nodosum secondary to other systemic causes. The presence of the erythema nodosum like lesion may be an indicator of the mildness of Behçet's disease; and the presence of histopathological evidence of severe vasculitis, especially phlebitis, in erythema nodosum-like lesions may be an indicator of the involvement of the gastrointestinal tract in Behçet's disease [1, 26, 27].

5.1.4. Papulopustular lesions (PPL)

PPL are cutaneous, sterile, folliculitis – or acne-like lesions on an erythematous base which appear as a papule and in the course of 24–48 h become a pustule. Trunk, buttocks, and the lower limbs are the most common localizations. Differential diagnosis of PPL is difficult from acne vulgaris. In a recent study, it is suggested that in BD patients the inflammatory lesions located on the face were less than those in the acne vulgaris. Inflammatory lesions such as folliculitis on the legs were only seen, in the BD group. The papulopustular lesions of BD could not be distinguished from AV by histology [1, 25, 28].

5.1.5. Superficial thrombophlebitis

Superficial thrombophlebitis is the most frequent type of venous involvement. The patients usually present with erythematous, tender, subcutaneous nodules arranged in a linear fashion.

The small vein can be palpated as a string-like hardening of the subcutaneous tissue with reddening of the overlying skin. It is more common in males and frequently confused with erythema nodosum like lesions. Superficial thrombophlebitis is often associated with other forms of vascular disease in BD [1, 25].

5.1.6. Other cutaneous lesions

Extragenital ulcerations clinically resemble aphthous lesions of the disease. They are recurrent and usually heal with scarring. The lesions have been reported on various locations such as the legs, axillae, breast, neck, interdigital skin of the foot, inguinal region, and neck.

Sweet syndrome like lesions are characterized by painful erythematous plaques and nodules which usually localize to face, neck, and extremities. Other cutaneous vasculitic lesions include pyodermagangrenosum-like, erythema multiforme-like lesions, palpable purpura, subungual infarctions, hemorrhagic bullae, furuncles, and abscesses [1, 3, 25].

5.1.7. Skin pathergy test

Pathergy phenomenon is defined as a state of altered tissue reactivity that occurs in response to minor trauma. A papule or a sterile pustule occurs 24–48 h after an intradermal injection of the skin with a 20-gauge needle. The positivity rate of pathergy test in BD was found to vary from country to country. It is most prevalent around the silk route, which extends from the Far East to the Mediterranean Basin. Other diseases that can be seen positive pathergy test are; pyodermagangrenosum, interferon alpha-treated chronic myeloid leukemia patients, Sweet's syndrome, eosinophilic pustular folliculitis, inflammatory bowel disease and healthy individuals [26, 29].

5.2. Ocular manifestations

Ocular involvement is one of the most disabling complications of BD, causing loss of vision that may progress to blindness if left untreated. The typical form of ocular involvement is a relapsing and remitting panuveitis and retinal vasculitis. Uveitis occurs in approximately two-thirds of BD patients. A single attack will usually heal spontaneously without a sequel. But destructive and recurrent attacks, especially with the posterior segment and retina involvement, may cause irreversible ocular structural changes and permanent damage in the sensory retina, resulting in loss of vision [30, 31].

5.3. Vascular involvement

Vascular involvement in BD includes venous thrombosis, arterial occlusion, and pulmonary artery and aortic aneurysm formation [32]. Lower extremity deep venous thrombosis is the most common form of vascular involvement in BD [9]. Venous thrombosis may occur at any site of the body and any size of vessels may be affected [26]. Inferior vena cava, superior vena cava, and pulmonary artery are the other common involved vessels. Pulmonary artery involvement, the most common form of arterial involvement, manifests as aneurysms and "in situ" thrombosis. Pulmonary artery involvement and Budd-Chiari syndrome are the leading

causes of increased mortality. In a vascular cluster, typically, several types of venous or arterial vascular involvement may accumulate in the same individual. Vascular involvement is more common and more severe among males [33].

5.4. Gastrointestinal involvement

Intestinal BD is characterized by ulcers on the gastrointestinal tract, usually at the ileocecal region. Patients can present with abdominal pain, diarrhea, constipation or acute abdomen due to perforation of an ulcer. To distinguish clinical symptoms of intestinal BD from inflammatory bowel disease may be difficult. Some colonoscopy and histopathological findings may help for differentiating the two disease [9, 26].

5.5. Neurologic involvement

Neurobehcet disease is a rare complication of BD. But it is an important cause of morbidity and mortality in BD. Little is known about this neuro-Behçet because there are no confirmed diagnostic criteria, and all the studies have a small number of patients. The prevalence reported normally ranges between 5 and 15% and it is more frequent amongst men between 20 and 40 years old. The typical presentations include focal parenchymal lesions, vascular thrombosis, arterial vasculitis, and aseptic meningoencephalitis [34].

5.6. Joint involvement

Joint manifestations are common in Behçet's disease. Most patients suffer from a nonerosive, nondeforming oligoarthritis typically involving the knees, ankles, and wrists [35].

6. Diagnosis

There is not a universally accepted pathognomonic test for diagnosis of BD. The diagnose is primarily based on clinical criteria and exclusion of alternative diagnosis [1]. Various criteria have been used. The mostly used one is International Study Group for Behçet's Disease criteria (ISG criteria) which formulated at 1990. According to ISG criteria, the presence of oral aphthosis was mandatory. Two of the following symptoms were required for the diagnosis of BD: Genital aphthosis, skin manifestations, ocular lesions, and positive pathergy reaction [36]. Later in 2006, a new set was proposed by the International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD). According to ITR-ICBD, oral aphthosis, skin manifestations, vascular manifestations, and positive pathergy reaction score one point each. Genital ulcers and ocular manifestations get two points each. The diagnosis of BD is made when three or more points are collected [37]. Then at 2013, the new criteria were revised under the name International Criteria for Behçet's disease (ICBD). In this criteria oral ulcer, genital ulcer, and ocular manifestations get each two points; skin lesions, neurological manifestations, vascular manifestations, and positive pathergy test get each one point. For the diagnosis, four points are required [38].

7. Prognosis

BD has a chronic course with unpredictable remissions and exacerbations. The diagnosis is difficult in many patients because there is not a universally accepted diagnostic criteria and the clinical symptoms may be seen in many other diseases. In a study from Germany, it was shown that because of the ethnicity, in Turkish patients, the diagnosis of BD is earlier than German patients. Because in German patients the diagnosis was later and more difficult than Turkish patients, some of the patients might be followed with the wrong diagnosis for long times. It is mentioned that the diagnosis is more difficult in non-endemic areas [39]. But recognizing the disease may permit early diagnosis and treatment. An oral ulcer is the most commonly seen clinical symptom followed by a genital ulcer, PPL, erythema nodosum like lesions and articular and ocular lesions. These clinical symptoms lead to pain and loss of function. On the other hand pulmonary especially large vessel involvement, neurological involvement, and bowel perforation are causes of mortality [1]. It is shown that male sex, arterial involvement, and a high number of BD flares were independently associated with the risk of mortality [40].

8. Conclusion

BD is a chronic inflammatory multisystem disease that affects any size of the vessels. The etiology is not clear yet. However, infectious and genetic factors are thought to act roles in the etiopathogenesis. There is no specific serological marker and the diagnosis of the disease depends on clinical criteria only. Moreover, the clinical symptoms of the disease may be seen in many diseases. So, knowing the findings, diagnostic criteria, prognosis, and complications of the disease provides the early diagnosis of the BD that is very important for the treatment of the disease, which has risks of mortality and morbidity. So, in this book, epidemiology, etiopathogenesis, cutaneous, and systemic findings and treatment of BD will be reviewed in detail.

Author details

Müzeyyen Gönül* and Selda Pelin Kartal

*Address all correspondence to: muzeyyengonul@gmail.com

University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Dermatology Clinic, Ankara, Turkey

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